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Pengfei Xu [a,b,c,d], Nicholas T. Van Dam [e], Marie-José van Tol [c], Xueyi Shen [f], Zaixu Cui [g], Ruolei Gu [h,i], Shaozheng Qin [f], André Aleman [a,c,j], Jin Fan [k,*], Yue-jia Luo [a,b,**]

[a] Shenzhen Key Laboratory of Affective and Social Neuroscience, Center for Brain Disorders and Cognitive Sciences, Shenzhen University, Shenzhen, 518060, China
[b] Center for Emotion and Brain, Shenzhen Institute of Neuroscience, Shenzhen, 518057, China
[c] Cognitive Neuroscience Center, Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, 9713 AW, Groningen, the Netherlands
[d] Great Bay Neuroscience and Technology Research Institute (Hong Kong), Kwun Tong, Hong Kong, China
[e] School of Psychological Sciences, University of Melbourne, Victoria, 3010, Australia
[f] National Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, 100875, China
[g] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, 19104, USA
[h] Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China
[i] Department of Psychology, University of Chinese Academy of Sciences, Beijing, 100049, China
[j] Department of Psychology, University of Groningen, the Netherlands
[k] Department of Psychology, Queens College, The City University of New York, Flushing, NY, 11367, USA

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ABSTRACT

Anxious individuals tend to make pessimistic judgments in decision making under uncertainty. While this phenomenon is commonly attributed to risk aversion, loss aversion is a critical but often overlooked factor. In this study, we simultaneously examined risk aversion and loss aversion during decision making in high and low trait anxious individuals in a variable gain/loss gambling task during functional magnetic resonance imaging. Although high relative to low anxious individuals showed significant increased risk aversive behavior reflected by decreased overall gamble decisions, there was no group difference in subjective aversion to risk. Instead, loss aversion rather than risk aversion dominantly contributed to predict behavioral decisions, which was associated with attenuated functional connectivity between the amygdala-based emotional system and the prefrontal control regions. Our findings suggest a dominant role of loss aversion in maladaptive risk assessment of anxious individuals, underpinned by disorganization of emotion-related and cognitive-control-related brain networks.

1. Introduction

Human decision making under uncertainty is always accompanied by risk. While avoiding potential risk can be functionally adaptive, excessive risk aversion may impair daily functions as has been noted for individuals prone to anxiety (Hartley and Phelps, 2012). Unfortunately, risk aversion is often confounded with loss aversion in decision making tasks, limiting our ability to determine the primary motivation for such behavior (Phelps et al., 2014). Whereas risk aversion can be defined as a general aversion to the uncertainty or variance in outcome regardless of whether the outcome is a potential gain or loss (De Martino et al., 2010), loss aversion refers to a tendency to overweight losses relative to equivalent gains regardless of the level of risk (Kahneman and Tversky, 1979). When risk is accompanied by a potential loss, individuals with high loss aversion may appear to be risk averse. Therefore, differentiating aversion to loss from aversion to risk in decision making is pivotal to understanding avoidance behavior in psychopathology, especially in anxiety.

Recent studies have shown that sensitivity to risk and loss can be measured and examined orthogonally in gambling tasks (for a review, see Phelps et al., 2014). Risk aversion can be quantified using computational models rather than just overall gamble decisions (risk-avoidant behaviors). One simple and quickly implemented model is the mean-variance

* Corresponding author. Department of Psychology, Queens College, The City University of New York, 65-30 Kissena Blvd., Flushing, NY, 11367, USA.
** Corresponding author. Shenzhen Key Laboratory of Affective and Social Neuroscience, Shenzhen University, 3688 Nanhai Ave., Nanshan District, Shenzhen, 518060, China.
E-mail addresses: jin.fan@qc.cuny.edu (J. Fan), luoyj@szu.edu.cn (Y.-j. Luo).

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approach, which postulates that preference is a function of risk (variance in the probability distribution of possible outcomes) and expected value (defined as mean of outcome probability distribution, D'Acremont and Bossaerts, 2008). However, this model is not able to measure risk aversion and loss aversion simultaneously because it collapses gain and loss across a single distribution. An alternative approach is to use expected utility models, which highlight the role of utility for each specific payoff and its state probability in decision making (Schonberg et al., 2011). The most prominent example, prospect theory (Kahneman and Tversky, 1979), posits that preference is a function of outcome probabilities and (directional) magnitudes of possible outcomes; in this model, a separate loss parameter permits dissociation of loss aversion from risk aversion.

Using this type of modeling, patients with amygdala damage have shown a dramatic reduction in loss aversion but relatively intact risk aversion, suggesting a crucial role of the amygdala in loss but not risk aversion (De Martino et al., 2010). Loss aversion, but not risk aversion, has been shown to be regulated by cognitive strategies, accompanied by reduced skin conductance responses (Sokol-Hessner et al., 2009), decreased activation of the amygdala-based emotional system, and increased activation in the cognitive control system (Sokol-Hessner et al., 2012). Consistently, loss aversion has been directly associated with exaggerated activation in the amygdala and its connectivity (Charpentier et al., 2015). Although both limbic (including the amygdala associated with bottom-up processing of primary emotional afferents) and prefrontal (associated with top-down control over primary emotional responses) systems have been shown to be aberrant in anxiety (Bishop, 2007), direct neural and behavioral evidence for the importance of loss aversion in decision making among anxious individuals is still lacking.

While individual differences in personality have been associated with differential motives to achieve or avoid failure (Atkinson, 1957), anxious individuals have shown generally avoidant behaviors (Bishop and Gagne, 2018; McNaughton and Corr, 2004). Unlike commonly observed alterations of executive functions across populations with elevated trait and pathological anxiety, risk-avoidant behaviors might be specific to pathological anxiety (Charpentier et al., 2016b). Altered loss aversion has been observed in individuals with pathological anxiety (Charpentier et al., 2016) and in adolescent anxiety (Ernst et al., 2014), depression (Huh et al., 2016), and greedy personality (Li et al., 2019). However, whether findings among those with pathological anxiety hold for healthy populations with varying levels of anxiety, as well as the potential role of the amygdala in these processes, remain unclear.

In this study, we examined the determinant roles of risk aversion and loss aversion during decision making, as well as roles of the amygdala and its connectivity with prefrontal control regions, in anxious individuals. We adopted a gambling task from a previous study (De Martino et al., 2010) to independently measure risk aversion and loss aversion, and examined associated brain activation and connectivity using functional magnetic resonance imaging (fMRI). We predicted that loss aversion would be the dominant predictor over risk aversion in decision making, and that augmented loss aversion but not risk aversion would be evident in high relative to low anxious individuals. We expected augmented loss aversion to be associated with dysconnectivity between amygdala-based (bottom-up/emotional) and prefrontal-based (top--down/control) neural systems in anxious individuals.

2. Methods and materials

2.1. Participants

Fifty-six healthy individuals (30 female, age = 21.18 ± 2.27, M ± SD) were selected from a pool of 384 participants based on trait anxiety assessed by a Chinese translation of State-Trait Anxiety Inventory (STAI-T; Shek, 1993; Spielberger et al., 1983). The sample consisted of 28 individuals with high trait anxiety (HA; STAI-T $\geq$ 45, $\geq$75th percentile) and 28 individuals with low trait anxiety (LA; STAI-T $\leq$ 35, $\leq$25th percentile). The sample sizes was determined based on previous studies of loss aversion (Charpentier et al., 2015, Charpentier et al., 2016; Sokol-Hessner et al., 2009). Given high comorbidity among anxiety and depression (Clark and Watson, 1991; Stavrakaki and Vargo, 1986), we included the Chinese version of the Zung self-rating depression scale (SDS; Shu, 1993; Zung et al., 1965). None reported a history of neurological or psychiatric disorders or head injury. Written informed consent was obtained from each participant. This study was approved by the Institutional Review Board of Beijing Normal University.

2.2. Task design

To independently measure the impact of loss/gain and risk conditions on decision making, we employed a risky decision making paradigm to manipulate the expected value and potential outcome variance (De Martino et al., 2010). In this paradigm, participants were asked to make decisions of whether to gamble. The gamble in each trial was composed of one of 16 potential gains ranging from +¥20 to +¥50 (displayed in green), and one of 16 potential losses ranging from -¥20 to -¥50 (displayed in red), both varied in an increment of ¥2 (Fig. 1).

Expected value (EV) was calculated as a function of the size and probability of potential gains (G, positive value) and losses (L, negative value): $EV = 0.5 \times G + 0.5 \times L$; large probable gain and small probable loss leads to high EV. Variance was measured as the square of the absolute difference between probable gains and losses: $VAR = (0.5 \times G - 0.5 \times L)^2$; large probable gain vs. large probable loss leads to high VAR. See Fig. 1 for the matrix of the decision space for EV and VAR. Each of the 256 (16 × 16) possible gain-loss pairs was presented once per subject.

The 256 trials were randomly divided across 2 sessions, each of which included 128 trials and lasted for approximately 8 min. Stimulus display and behavioral data acquisition were conducted using E-Prime software (Version 2.0, Psychology Software Tools, Inc., Pittsburgh, PA, USA). One week before the experiment, each participant was given ¥50 in cash as an initial endowment and was informed that the final payment would be made at the end of the experiment according to the sum of the initial endowment and their gains/losses from an actual decision in a randomly selected trial during the experiment. This procedure was used to maximize participant consideration of each trial and ensure that each decision was made independently (De Martino et al., 2010; Tom et al., 2007). All participants completed a practice version to gain familiarity with the task before scanning.

2.3. Behavioral models and estimates of risk and loss aversion

In general, for model-free behavioral analyses, we compared the distribution of gamble decisions, probability of gamble decisions, and its changes associated with EV and VAR respectively between two groups. Next, we compared the goodness-of-fit of two models to explain decisions among anxious individuals. While the mean-variance model was able to differentiate contributions of risk variance from objective expected value, risk aversion and loss aversion were confounded. Thus, we used prospect theory model to obtain independent estimates of risk and loss attitudes.

To assess the similarity among the distribution of decision matrix and the distributions of EV and VAR matrix, similarity structural indexes (Wang et al., 2004) were calculated. A non-parametric bootstrapping method (Mooney, 1993) was applied to test the significance of the similarity. To assess sensitivity to risk, we first used regression models to measure the gamble rates as a function of variance. Probability of gamble selection for choices sharing the same gamble variance as the dependent variable was regressed on VAR as an independent variable in each group. The slope (β) of this regression was defined as the estimate of risk aversion. The indifference point between accept and reject a gamble (i.e., the EV with an acceptance rate of 50%) was also calculated by fitting the EV with a logistic regression model as the independent variable and participants' choices as the dependent variable.

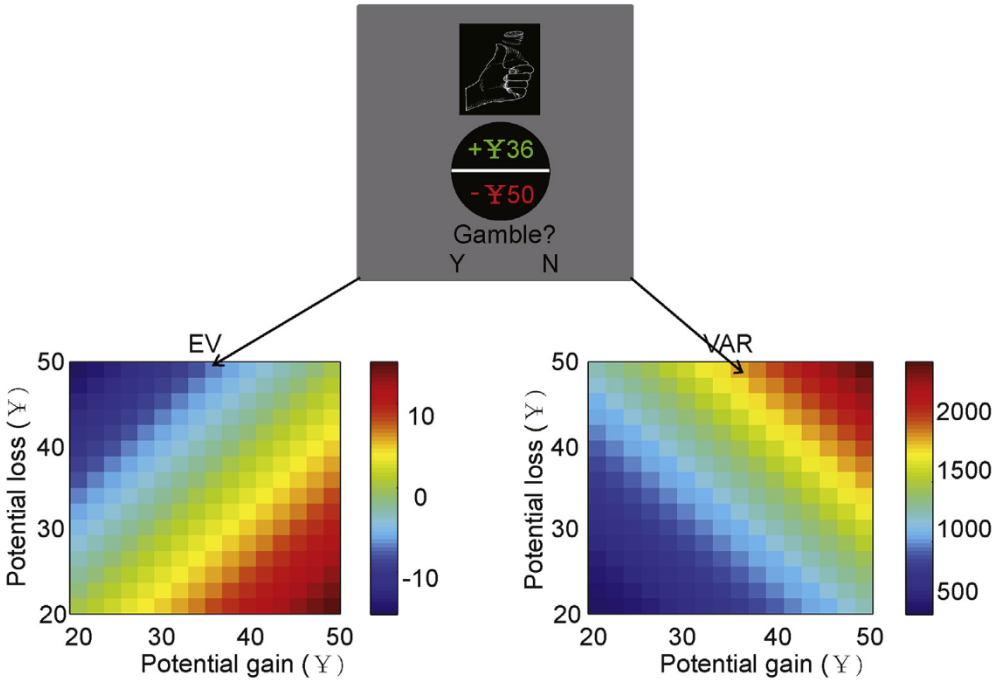

Fig. 1. *Task design.* Top of the figure shows an example trial. During each trial, an image displaying two options (gamble or not gamble) was presented for 3s with an inter-trial-interval at 400 ms–1600 ms. There was an equal probability (50%) of gaining or losing a certain amount of money for the gamble option. If participants chose not to gamble, there was no reward or penalty. Omitting a response during the 3s window resulted in a penalty of ¥2. Bottom of the figure shows matrices of the decision space, displaying EV (on the left) and VAR (on the right) of the trials as a function of potential gain (x axis) and loss (y axis). EV: expected value; i.e., relative assessment of probable outcome as a function of gain relative to loss. VAR: variance; i.e., the square of absolute difference between probable gains relative to losses. Heat index: red: high value; blue: low value.

We measured risk aversion by applying the mean-variance approach (Schonberg et al., 2011). The value of a risky option is calculated as a trade-off between the EV and VAR (D'Acremont and Bossaerts, 2008)

$$\nu(gamble) = EV - \beta\, VAR \tag{1}$$

where β reflects a penalty for risk, and $\beta > 0$ indicates risk avoidance.

Risk and loss aversion were estimated simultaneously in a three-parameter model (Sokol-Hessner et al., 2009, 2012) using the power value function from prospect theory (Kahneman and Tversky, 1979).

$$\nu(x^{+}) = x^{\gamma} \tag{2}$$

$$\nu(x^{-}) = -\lambda(-x)^{\gamma} \tag{3}$$

$$P = \frac{1}{\left(1 + e^{-\mu(\nu(gamble) - \nu(guaranteed))}\right)} \tag{4}$$

where x is the absolute amount of potential gain or loss, $\nu(x^{+})$ and $\nu(x^{-})$ represent the subjective value of potential gain or loss, respectively, gamma (γ) indicates risk aversion (diminishing sensitivity to changes in value as the absolute value increases). While $\gamma > 1$ represents risk seeking, $\gamma < 1$ indicates risk aversion and a small value of γ (i.e., approaching 0) indicates high risk aversion. The lambda (λ) represents subjective weighting of losses (relative to gains). A high value of λ indicates high loss aversion. Mu (μ) refers to the consistency of participants' choices. P is the acceptance rate of gamble.

Both of these two models were fitted at the individual level. To avoid attraction to local minima, all parameters were estimated multiple times for each participant with varying initiation points. We conducted model comparison using Bayesian information criterion (BIC) scores (Haughton, 1988), which is an approximation of the model evidence, with lower BIC scores indicating higher model evidence or better model fit. To test the contributions of risk aversion and loss aversion to behavioral decisions, multiple regression analyses were performed with gamble acceptance as the dependent variable, and with γ, λ, and group as independent variables, respectively.

Two-sample *t*-tests were performed to examine group differences on overall gamble rates and reaction times. To test whether high anxious individuals were more risk or loss aversive than those low in trait anxiety, one-tailed two-sample *t*-tests were performed. To further assess whether group difference in risk and loss aversion would support the alternative or null hypothesis, we calculated Bayes factors (BF) to determine the strength of evidence for the alternative hypothesis relative to the null hypothesis (Dienes, 2014). The independent-sample *BF t*-test was performed using the Bayes factor package (version 0.9.2+; http://bayesfactorpcl.r-forge.r-project.org/). To test the associations between anxiety and risk and loss aversion, a multiple regression analysis was performed with group as the dependent variable, and with the γ and λ as independent variables.

2.4. Imaging data acquisition and analysis

MRI data were acquired on a 3T Siemens MAGNETOM Trio MR system at Beijing Normal University, using a 12-channel phased-array head coil. The fMRI data were acquired using gradient-echo echo-planer imaging (EPI) with the following parameters: TR = 2 s, TE = 30s, 33 slices, 3.5 mm thick, 0.7 mm gap, flip angle = 90°, field of view = 200 × 200 mm, matrix = 64 × 64. A total of 584 volumes were acquired over a period of 20 min. In each of the two runs, 292 volumes were acquired. A high resolution 3D structural brain image was acquired for each participant using a T1-weighted MPRAGE sequence: TR/TE = 2530 ms/3.39 ms, flip angle = 7°, data matrix = 256 × 256, FOV = 256 mm × 256 mm. Image data analysis was conducted using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Image preprocessing, including slice-timing correction, realignment, co-registration, spatial normalization to a standard MNI template, resampling to 2-mm isotropic voxels, and spatial smoothing (with a Gaussian kernel of 8 mm FWHM), was performed.

General linear modeling (GLM) analyses with two models were conducted at the individual level. To identify brain responses to risk variance, we modeled the onsets of all trials as a single regressor and risk variance as a parametric modulation regressor. To access neural responses to expected value, objective EV was entered in another GLM as a parametric modulation regressor. To determine brain regions associated with potential gain and loss, respectively, as in a previous study (Tom et al., 2007), we also modeled onsets of all trials as a single regressor, as well as two parametric modulation regressors (the magnitudes of the

potential gain and of potential loss). Group (second) level statistical analyses were then conducted. For risk variance and expected value, one-sample tests were performed to test brain activation across two groups and two-sample *t*-tests were conducted to test group differences. For the model of potential gain and loss, a 2 (Group, HA vs. LA) × 2 (Outcome, potential gain vs. loss) ANOVA was performed with Group as a between-subjects factor and Outcome as a within-subjects factor .

2.5. Psychophysiological interaction (PPI) analyses

Given that the amygdala plays a central role in the processing of emotion, reward, and interactions between them (Baxter and Murray, 2002; LeDoux, 2007; Murray, 2007), psychophysiological interaction (PPI) analyses with the amygdala as the seed region were conducted to examine whether modulations of potential gain vs. loss were associated with the between group difference in connectivity of the amygdala. Blood-oxygen-level-dependent (BOLD) time-series data of the amygdala was extracted using a bilateral amygdala mask of the AAL atlas from the contrasts of potential gain vs. loss in the first-level GLM analysis. For each participant, a PPI model was built with regressors of i) the interaction between amygdala activity and Outcome (potential gain vs. loss) , ii) the main effect of amygdala activity, and iii) the main effect of Outcome (potential gain vs. loss), corresponding to PPI. ppi, PPI.Y, and PPI.P in the design matrix. A 2 (Group, HA/LA) × 2 (Outcome, potential gain/loss) ANOVA was then performed to test the interaction between Group and Valence in amygdala-based connectivity. All neuroimaging maps were thresholded at $p < 0.001$ corrected for multiple comparison using probabilistic threshold-free cluster enhancement (pTFCE) to avoid an arbitrary primary cluster-defining threshold (Smith and Nichols, 2009; Spisák et al., 2019).

To explore the contributions of brain functional connectivity to behavioral decisions, we conducted regions of interest (ROIs) analyses by extracting peak value of parameter estimates from significant clusters based on the results of functional connectivity analysis. Neuronal effect (in connectivity) of loss aversion was defined as differences of parameter estimates of potential gain subtracted from potential loss (λ') (see also Canessa et al., 2013; Charpentier et al., 2015; Li et al., 2019; Tom et al., 2007). Multiple regression analyses were performed with gamble acceptance as the dependent variable, and with γ, λ, λ' and group as independent variables.

2.6. Dynamic causal modeling (DCM) analyses

DCM analyses were implemented to examine the direction of the connectivity and modulatory effect of loss aversion. These effects were modeled by a differential equation, as previously defined (Friston et al., 2003). The state ($\dot{z}$) of the target region was predicted by the intrinsic connectivity with the source region (Az), the experimental modulation onto the connectivity (uBz), and the direct input into the model (Cu).

ROIs were defined as 6-mm-diameter spheres around each individual's peak voxel within the clusters/hubs of the amygdala-centered network (loss > gain condition). Search volumes for these contrasts were clusters defined in the group contrast in the PPI analysis. Model estimation at the individual level was conducted to evaluate the parameters of effective connectivity. One-sample and two-sample *t*-tests at the group level were performed to determine statistical significance. The Bonferroni procedure was used to correct for multiple comparisons (Dunn, 1961).

3. Results

Participants with gamble selection rates and reaction times beyond two standard deviations of the mean were excluded from data analyses (Cousineau and Chartier, 2010; Ratcliff, 1993; Rousseeuw and Hubert, 2011). As a result, there were 23 individuals in the high anxiety (HA) group (10 females, age = 21.22 ± 2.19 years, M ± SD) and 22 in the low anxiety (LA) group (12 females, age = 21.55 ± 1.41 years) included for final data analyses.

3.1. The behaviorally dominant contributor to decisions

The percentage of gamble choices for each trial is visualized as a 16 × 16 matrix across groups, within HA and LA, separately, and for group difference (Fig. 2). A similarity analysis showed that the similarity structural index (SSI) between the distribution of expected value (EV) matrix and decision matrix was significantly higher than random level in all groups (bootstrapping $ps < 0.001$ for across groups, within HA and LA; $p = 0.04$ for group difference; Fig. 2), the SSI between the distribution of variance (VAR) matrix and decision matrix was significantly higher than random level across groups ($p = 0.01$; Fig. 2A) and in HA ($p = 0.04$; Fig. 2B), and the SSI between EV and decision matrices were significantly higher than the ones between VAR and decision matrices in all groups ($ps < 0.001$; Fig. 2). These results indicate that the distribution of decisions is more consistent with EV than VAR.

Model comparison showed that the three-parameter prospect-theory model was the best model with the lowest Bayesian Information Criterion (BIC) scores (Table 1). Based on the winning model of prospect theory, $\log(\gamma)$ was not significantly correlated with log (λ) ($r = -0.23$, $p = 0.12$). In contrast, $\log(\beta)$ from the mean-variance was positively correlated with log (λ) ($r = 0.49$, $p < 0.001$). Multiple regression showed that across groups, loss aversion (λ), but not risk aversion (γ), significantly predicted behavioral decisions. All models involving λ were significant. Although γ alone could not predict behavioral decision, the involvement ofγsignificantly improved the prediction of the model when accompanied by λ(see Models 1–7 in Table 2). These results suggest that loss aversion is the dominant predictor of behavioral decisions, though risk aversion has additional predictive utility.

3.2. Heightened loss aversion but not risk aversion in high anxiety individuals

The two-sample *t*-test showed that overall gamble rates in HA were significantly lower than those in LA ($t\ (43) = -2.13$, $p = 0.04$; Fig. 3A), but no significant differences were observed in reaction times ($t\ (43) = 0.58$, $p = 0.56$; Fig. 3B). There was no significant group difference found for indifference point ($t\ (43) = 1.09$, $p = 0.28$; Fig. 3C). A regression model of outcome variance showed that risk aversion of HA was not significantly different from that of LA ($t\ (43) = 0.76$, $p = 0.45$; Fig. 3D). Results of *BF t*-test showed that BF was approximately equal to 1/3 ($BF_{\text{independent-sample}} = 0.36$), indicating support for the null hypothesis of equivalence in risk aversion between groups.

Based on the prospect-theory model, risk aversionγ was not significantly different between the groups ($t\ (43) = -0.88$, $p = 0.40$; Fig. 3E), whereas λ of HA was significantly higher than in LA ($t\ (43) = 1.80$, $p = 0.04$; Fig. 3F), indicating greater loss aversion in HA. The multiple regression model showed that loss aversion was a significant predictor of group ($t\ (43) = 2.36$, $p = 0.02$), but risk aversion was not ($t = -1.73$, $p = 0.09$). Although levels of depression were significantly correlated with trait anxiety across groups ($r = 0.79$, $p < 0.001$), the regression model with group as dependent variable and both of anxiety and depression as regressors showed that anxiety was a significant predictor ($t\ (43) = 10.08$, $p < 0.001$), but not depression ($t\ (43) = -0.64$, $p = 0.52$). Together with the regression model of outcome variance, the results provide robust evidence of heightened loss aversion but no difference in risk aversion for HA relative to LA.

3.3. Brain responses to potential gain and loss

GLM with magnitude of the potential gain and loss as parametric regressors, revealed comparable brain areas associated with activation as magnitude of potential gain and attenuation as magnitude of potential loss across groups. These areas included bilateral medial prefrontal

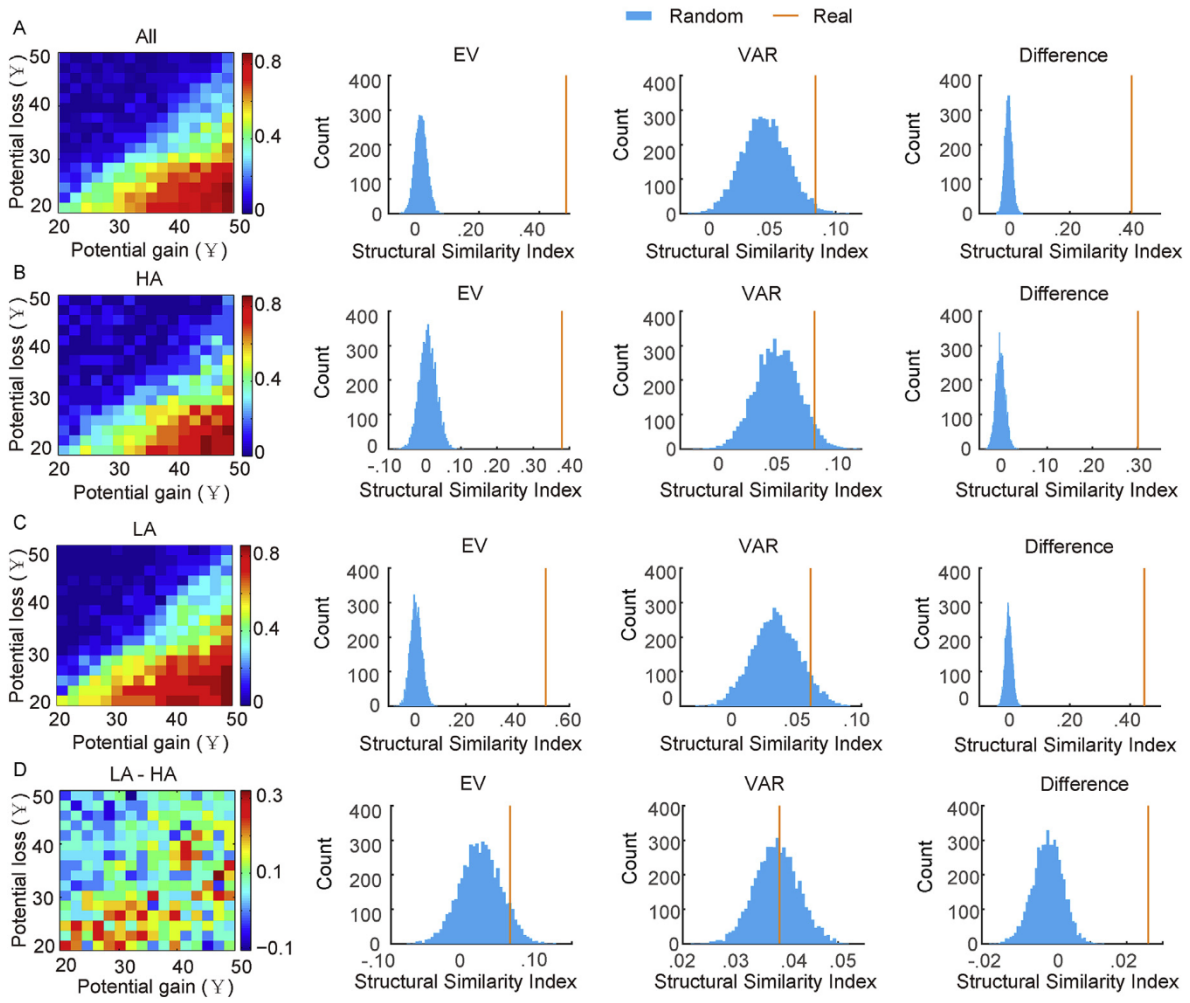

Fig. 2. *Decision distributions and similarity*. The first column reflects distributions of gamble rates at each level of potential gain vs. loss in all subjects (row A), high anxiety (HA; row B), low anxiety (LA; row C) and group difference (LA-HA; row D). Heatmaps indicate the rate of gamble selection (red: high; blue: low). The second through fourth columns display histograms of similarities and difference (Diff) of similarities among the behavioral distributions and design spaces of EV, VAR. The random distribution was generated by the bootstrap procedure (see Methods for more details).

Table 1
Comparison of model fit across mean-variance and prospect-theory models.

Model description	Number of parameters	BIC
Model 1: β	1	8196
Model 2: λ	1	14925
Model 3: γ	1	14488
Model 4: μ	1	14524
Model 5: γ, λ	2	7607
Model 6: μ, λ	2	7642
Model 7: μ, γ	2	14608
Model 8: μ, γ, λ	3	**7557***

Note: * Winning model (lowest BIC).

Table 2
Prediction of gamble decisions by different parameters.

Independent variables	Number of parameters	R^2	F	p	ΔF^1	Δp
Model 1: group	1	0.10	4.52	0.039	–	–
Model 2: γ	1	0.07	3.17	0.082	–	–
Model 3: λ	1	0.14	7.04	0.011	–	–
Model 4: λ, γ	2	0.33	10.45	<0.001	9.73	0.003
Model 5: group, γ	2	0.15	3.57	0.037	2.16	0.149
Model 6: group, λ	2	0.19	4.85	0.012	4.18	0.046
Model 7: group, γ, λ	3	0.34	7.16	<0.001	9.67	0.003
Model 8: λ'	1	0.19	10.08	0.003	–	–
Model 9: λ, λ'	2	0.28	8.01	0.001	8.32	0.006
Model 10: λ, λ', γ	3	0.42	9.98	<0.001	7.01	0.011
Model 11: group, γ, λ, λ'	4	0.43	7.46	<0.001	3.37	0.073

Note: ΔF and Δp are the F value and p value for the change between models (each given model compared with the prior model).λ' indicates neural loss aversion, which was defined as the functional connectivity between the amygdala and dlPFC modulated by the interaction between groups and potential gains and losses.

cortex (mPFC), vlPFC, dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), anterior insula (AI), ventral and dorsal striatum, and inferior parietal lobule (IPL; Fig. 4A; Tables S1 and S2). In contrast, a greater activation of loss vs. gain was observed in the amygdala (Fig. 4B; Tables S1 and S2).

For risk variance and expected value, there were no significant brain activations using the pTFCE threshold. For the sake of exploration, we used a lenient threshold that combined height ($p < 0.005$) and extent (20 voxels) threshold (Lieberman and Cunningham, 2009), which revealed negative associations of activations in bilateral ventral striatum with risk variance (Figure S1) and greater responses of right vlPFC, superior temporal gyrus (STG) and amygdala to potential gain and loss in HA (Figure S2).

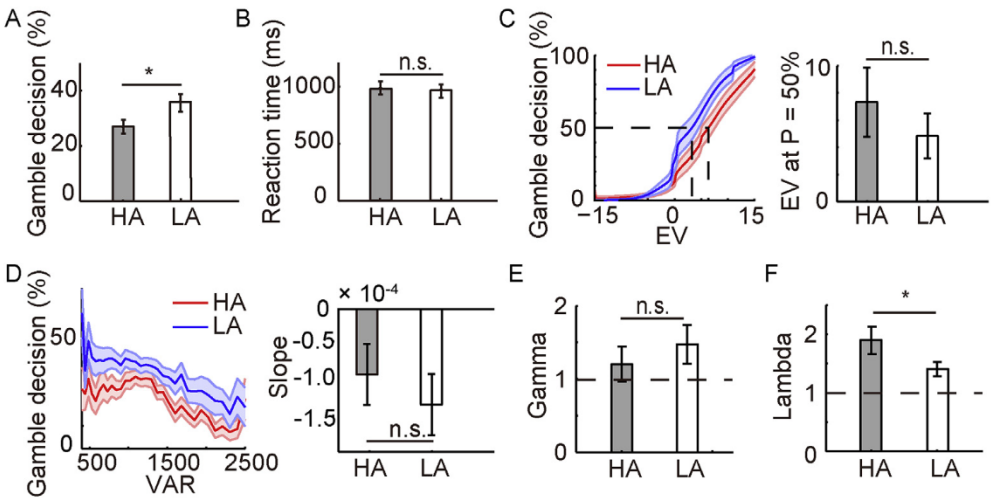

Fig. 3. *Behavioral group differences.* Group comparison of A) probabilities of gamble selection, B) reaction time, C) indifference point, D) sensitivity to variance and E) loss aversion parameter estimates lambda (λ) and risk aversion parameter estimates (-γ) in HA vs. LA. *$p < 0.05$. Data are presented as M ± SEM.

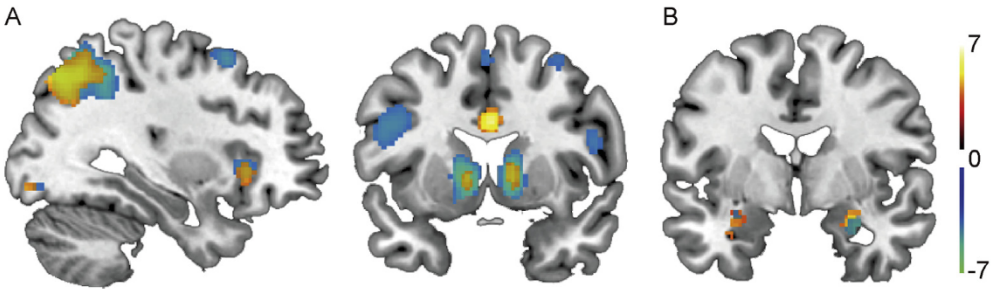

Fig. 4. *Brain responses to potential gain and loss.* A) Increased parametric responses to size of potential gain (red) and decreased parametric responses to size of potential loss (blue). B) Deactivation of right amygdala for potential gain (blue) and activation of bilateral amygdala for potential loss (red; an amygdala mask from AAL template was applied for visualization).

3.4. Group difference in functional connectivity between the amygdala and prefrontal areas in resposne to potential loss vs. gain

With potential gain or loss as the psychological context and the BOLD signal of the amygdala as the physiological context (Fig. 5A). Psycho-physiological interaction (PPI) analyses revealed an interaction between Group (HA/LA) and Outcome (potential gain vs. loss) in task-dependent connectivity of the amygdala with right dlPFC (Fig. 5B; MNI coordinates, x = 46, y = 24, z = 42; Z = 4.47, $p < 0.001$, $k = 145$). The coupling of the amygdala with the dlPFC was significantly more negative for assessing potential loss than gain in HA, but not in LA; functional connectivity between the amygdala and the dlPFC was significantly more positive for potential gain, whereas the coupling between the amygdala and the dlPFC was significantly more negative for potential loss estimation in HA than in LA (Fig. 5 C). With a lenient threshold of combined height ($p < 0.005$) and extent (20 voxels) threshold, it was also revealed that

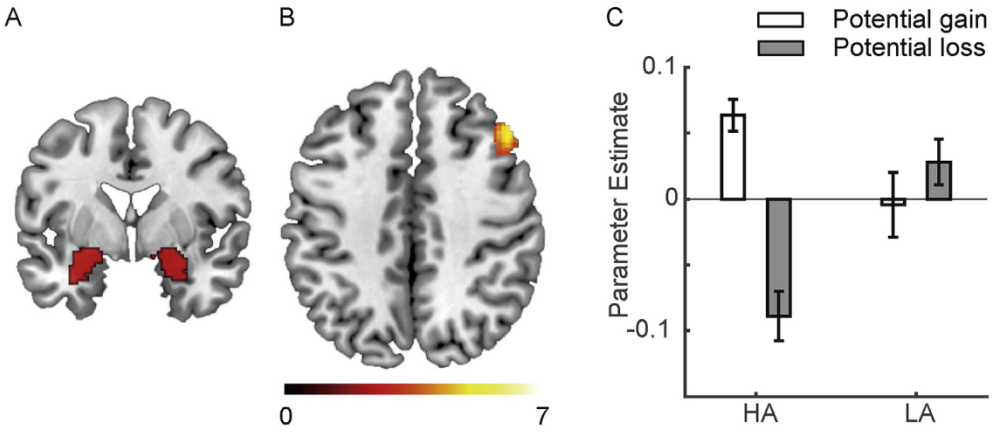

Fig. 5. *Alterations in amygdala-based connections in high anxiety (HA) compared to low anxiety (LA) during decision making.* A) An amygdala mask from AAL was applied to define the seed region for PPI. B) Changes of the amygdalar connectivity with right dorsal lateral prefrontal cortex (dlPFC) the interaction between Outcome (potential gain vs. loss) and Group (HA/LA); C) Reponses of dlPFC for potential gain and loss in HA and LA, respectively. Bars indicate M ± SEM.

connectivity of the amygdala with the IPL, vlPFC, STG, and right caudate was significantly more negative for assessing potential loss than gain in HA (Figure S3). These results point to a shift from positive to negative connectivity between the amygdala and prefrontal areas in response to processing potential loss vs. gain in HA but not in LA, which suggests increased emotional sensitivity and maladaptive cognitive control in HA.

3.5. Neural contributors to behavioral decisions in anxiety

Results showed that group, behavioral loss aversion (λ), and neural loss aversion (λ'), but not risk aversion (γ) significantly predict behavioral decisions. All the models involving λ were significant. Although γ alone could not predict behavioral decision, the involvement of γ significantly improved the prediction of the models when accompanied by λ (see Models 8–11 in Table 2). These results suggest that loss aversion is the dominant predictor at both the behavioral and neural level.

3.6. Increased bottom-up connectivity between the amygdala and right dlPFC in HA than LA

The Results of DCM analyses showed significantly positive reciprocal intrinsic connectivity between the amygdala and right dlPFC ($t = 9.47$, $p_{uncorrected} < 0.001$ for bottom-up (forward) connections from the amygdala to right dlPFC, and $t = 9.10$, $p_{corrected} < 0.001$ for top-down (backward) connections from right dlPFC to the amygdala; Fig. 6A). Compared to LA, HA showed significantly increased intrinsic connectivity from the amygdala to right dlPFC ($t = 2.69$, $p_{uncorrected} = 0.02$; Fig. 6B) and marginally decreased intrinsic connectivity from right dlPFC to the amygdala ($t = 1.78$, $p_{uncorrected} = 0.08$). These results indicated that during the task, there were enhanced communications in both the bottom-up (forward) connections from the amygdala to right dlPFC and top-down (backward) connections from right dlPFC to the amygdala. More importantly, bottom-up information (from the amygdala to right dlPFC) was enhanced in anxious individuals when making choices between both potential losses and gains.

4. Discussion

Despite numerous studies examining risk aversion and loss aversion (Admon et al., 2012; Albert and Duffy, 2012; De Martino et al., 2010; Phelps et al., 2014; Sokol-Hessner et al., 2009; Tom et al., 2007), their relationship to each other and contributions to behavioral decisions were unclear. Our results showed that loss aversion but not risk aversion is dominant in predicting behavioral decisions, especially in anxious individuals. Despite of less gamble decisions in anxious individuals, no group difference was found in subjective aversion to risk. In contrast, we found heightened loss aversion in high anxious individuals during risk decision making. Our results thus suggest that the negative decision bias in anxiety is due to an overweighting of loss rather than risk. Given that risk and loss aversion were in general not modeled independently in previous studies of risk decision making in anxiety (for a review, see Phelps et al., 2014), high risk avoidant behaviors of anxious individuals in those studies may be attributed to loss aversion rather than their risk attitudes.

Because anxiety has been associated with increased bottom-up, stimulus-driven processing (Eysenck et al., 2007) and decreased top-down, goal-directed processing (Bishop, 2007), the heightened loss aversion in HA is likely driven by attenuated top-down affective control over augmented bottom-up emotional processing when assessing uncertain gain/loss outcomes, with an asymmetric emphasis on potential loss. Additionally, the amygdala-caudate connectivity was found to be decreased in response to loss and increased in response to gain in HA, possibly reflecting asymmetric coupling of reward and punishment estimation, consistent with exaggerated approach-avoidance conflict commonly observed in anxious individuals (Stein and Paulus, 2009). An integrative explanation is that dysfunctional top-down and bottom-up systems jointly contribute to risk decision making in anxiety, leading to increased awareness of and/or sensitivity to potential loss, which in turn results in an overestimation of the likelihood of loss.

Neuroimaging findings support the hypothesis that both bottom-up (especially affective processing) and top-down (especially emotion regulation) biases contribute to decision making among anxious individuals. The increased responses to potential loss but decreased responses to potential gain in the amygdala and ventral attention network of high anxious individuals indicate the neural substrates of increased emotional and attentional engagement to perceived loss over gain. These results suggest that augmentation of the asymmetry between reward and punishment in anxiety may include a bias towards perceived loss or punishment, as well as decreased sensitivity to gains. The amygdala, a core region of the emotional brain (LeDoux, 2000), has been shown to be hyperactive in anxious individual (Davis, 1992) and is pivotal in the generation of loss aversion (De Martino et al., 2010). The ventral attention network, encompassing portions of the vlPFC and ventral STG (Corbetta and Shulman, 2002), has been associated with bottom-up stimulus-driven attentional processing (Corbetta et al., 2008). Previous studies have indicated that an overactive ventral attention network during bottom-up related processing is related to elevated anxiety (for a review, see Sylvester et al., 2012). Given that the processes related to loss aversion tend to operate automatically (Kermer et al., 2006), increased aversion to potential loss in anxious individuals could be partially driven by enhanced bottom-up processing with heightened amygdala activity for threat. Thus, these results provide neurobehavioral evidence consistent with the hypothesis of increased attention to loss among anxious individuals when assessing gambling options. Given the role of the caudate in the evaluation of reward processing (Haruno et al., 2004; Knutson et al., 2005; Tanaka et al., 2004), positive or negative functional coupling of the amygdala with the caudate modulated by potential gain or loss suggests a devaluation of gain but overvaluation of loss in anxious individuals (see also Charpentier et al., 2015). This is consistent with the idea that behavioral loss aversion is related to the influence of the negative anticipatory response on the computation and evaluation of potential outcome (De Martino et al., 2010). These results likely reflect the neural substrates of increased avoidance to loss and decreased approach to gain, both of which contribute to deficits of computation and evaluation of anticipated outcomes in anxiety.

Reduced connectivity between the amygdala and top-down prefrontal control areas is also a candidate contributor to heightened loss aversion. The frontoparietal network (including parts of dlPFC and IPL), referred to as the executive control network (Fan et al., 2014; Seeley et al., 2007), is involved in adaptive adjustments to achieve general goals (Dosenbach et al., 2008). A large body of evidence has shown that decreased functioning of frontoparietal networks are linked to impaired attentional or inhibitory control in both clinical and nonclinical anxiety (for a review, see Sylvester et al., 2012). The dlPFC and dlPFC-amygdala pathway are also involved in successful regulation of negative emotion (Davidson et al., 2000; Lee et al., 2012; Ochsner et al., 2004; Taylor and Liberzon, 2007). Dysconnectivity of the amygdala with prefrontal control network has been consistently shown in recent meta-analysis of anxious brain networks (Xu et al., 2019), while connectome-based predictive model of anxiety has shown the importance of the intrinsic subcortical-prefrontal connectivity in predicting trait anxiety (Wang et al., 2020). Because loss aversion could be reduced by intentional cognitive regulation strategies (Sokol-Hessner et al., 2009), the present results may indicate an attenuation of inhibitory control to override competing loss estimation in anxious individuals.

The ability of amygdala-dlPFC connectivity (in relation to loss aversion) to predict behavioral decisions and decreased connectivity of this circuit in high anxiety suggests a potential abnormality in anxious individuals. While low anxious individuals seemed to exhibit effective inhibitory control of the dlPFC over the amygdala for analytic selection during trials with potential losses, this regulatory effect was attenuated in anxious individuals. Our results also support the homeostatic hypothesis

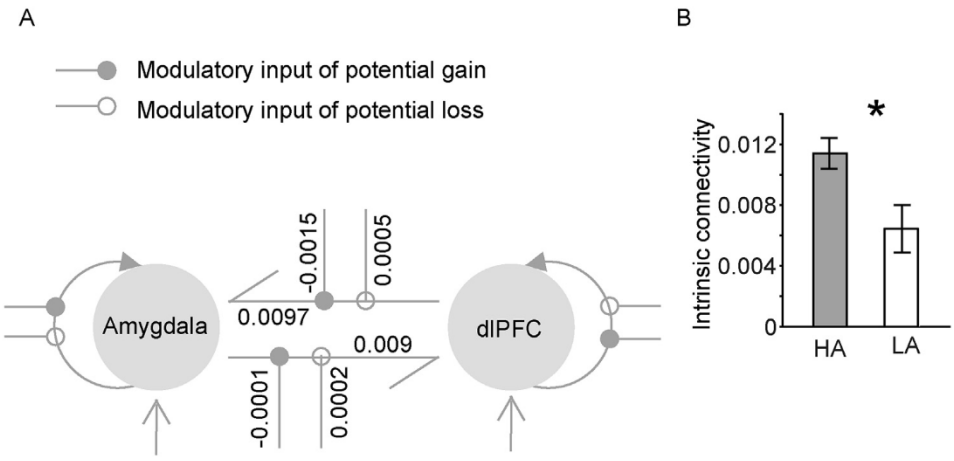

Fig. 6. The model and results of DCM analysis. A) The model with full reciprocal connectivity between the amygdala and right dlPFC. B) Compared to LA, HA showed significantly increased intrinsic connectivity from the amygdala to dlPFC.

of decision making dysfunctions in psychiatry which proposed that maladaptive responses of psychiatric patients result from an unstable homeostatic balance underpinned by brain systems for multiple bottom-up and top-down processes (Paulus, 2007). Increased intrinsic connectivity from the amygdala to right dlPFC and marginally decreased intrinsic connectivity from right dlPFC to the amygdala suggest miscommunications between the amygdala and dlPFC in anxious individuals, characterized by strengthened bottom-up information afferents and weakened top-down affective control systems. Consistent with preclinical work of anxious temperament (Birn et al., 2014), these findings suggest that amygdala-dlPFC coupling is important for decision making (with an overemphasis on loss aversion), wherein increased bottom-up emotional and decreased top-down control processes underpin anxious behavior.

Interestingly, a recent study found enhanced risk aversion but equivalent loss aversion in pathologically anxious individuals relative to controls (Charpentier et al., 2016). Together with our results, these findings suggest potentially different decision preferences and patterns between subclinical and clinical populations of anxiety. Another potential explanation might be that a different task manipulation was used in that study. Despite that a similar gambling paradigm was adopted, participants were also asked to simultaneously complete an emotional memory task, which might divert cognitive resources for risk and value evaluation during decision making and result in decisions based on superficial risk. Additionally, the correlation between risk aversion and loss aversion was observed in the mean-variance model (consistent with Canessa et al., 2013) but not prospect theory model (consistent with Charpentier et al., 2016) in the present study. The differentiation in these correlations between models suggests that risk aversion, as defined by the mean-variance model, might be partially explained by loss aversion, while the prospect theory model may be able to independently measure loss aversion and risk aversion. Taken together, our results suggest distinctive neurocognitive mechanisms between risk aversion and loss aversion.

Consistent with previous studies (Christopoulos et al., 2009; Krain et al., 2006; Schultz et al., 2011), we found that responses of the bilateral ventral striatum and vlPFC were associated with risk variance. However, there was no association between risk and activity in the insula, a brain structure which has shown an important role in risk processing (Mohr et al., 2010; Preuschoff et al., 2008) and anticipatory anxiety (Engelmann et al., 2015). One explanation might be that we controlled for risk probability to be fixed across conditions at 50% in the current study, to which the insula is sensitive (Christopoulos et al., 2009). Given that risk, defined as outcome variance in the present study, consists of variations in outcome magnitude and probability, these results suggest separate neural underpinnings for these components of risk (Berns and Bell, 2012; Shenhav and Greene, 2010; Smith et al., 2009).

Declaration of competing interest

The authors declare no competing financial interests or potential conflicts of interest.

CRediT authorship contribution statement

Pengfei Xu: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Nicholas T. Van Dam:** Investigation, Methodology, Writing - review & editing. **Marie-José van Tol:** Investigation, Writing - review & editing. **Xueyi Shen:** Investigation, Data curation. **Zaixu Cui:** Investigation, Methodology. **Ruolei Gu:** Investigation, Writing - review & editing. **Shaozheng Qin:** Investigation, Writing - review & editing. **André Aleman:** Investigation, Writing - review & editing. **Jin Fan:** Conceptualization, Methodology, Writing - review & editing. **Yue-jia Luo:** Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116957.

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